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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,525	03/18/2002	Robert D. Simari	07039-280001	5964

7590 04/20/2005

Fish & Richardson
Suite 3300
60 South Sixth Street
Minneapolis, MN 55402

EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,525	SIMARI, ROBERT D.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,5-29 and 31-46* is/are pending in the application.

4a) Of the above claim(s) *5-16,24 and 31-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,17-23 and 25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/10/05*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date 2/4/05.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

HC

DETAILED ACTION

Non-Final Rejection

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/10/05 has been entered.

Claims 3, 5-29, and 31-46 are pending.

Applicant's traversal and the amendment to claims 28 and 29 in paper filed on 2/10/05 is acknowledged and considered.

Election/Restrictions

Claims 5-16, 24, and 31-46 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/14/04.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 2/10/05 is being considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 17-23, and 25-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing brain natriuretic peptide (BNP) levels to establish whether overexpression of BNP delays the progression of asymptomatic left ventricular dysfunction (ALVD) to overt congestive heart failure (CHF) in a canine ALVD model comprising intracoronary delivery to the canine a composition comprising a nucleic acid encoding BNP operatively linked to a promoter in a delivery vehicle and determining whether the increase of BNP delays the progression of ALVD in the model, does not reasonably provide enablement for a method of increasing BNP in a mammal comprising administering a composition comprising a nucleic acid encoding a brain natriuretic peptide operably linked to a promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to a method to increase BNP levels in a mammal, comprising: administering to the mammal a composition comprising a nucleic acid molecule comprising a nucleic acid sequence comprising a nucleic acid segment encoding a BNP or a chimera thereof in a delivery vehicle. In view of the specification (see abstract and pages 4 and 45-50), one skilled in the art would determine that the only uses for increasing BNP in a mammal would be for determining the result of the increase of BNP in the mammal in an organ or for use

in a method of inhibiting or preventing heart failure in a mammal or to relax cardiac muscle in a mammal.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (United States v. Technologies Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather a conclusion reached by many factors. These factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in In Re Wands (see above).

The broadest claims read on increasing BNP in a mammal and determining the result of the increase of BNP in the mammal. In addition, natriuretic peptides (NP) are known in the prior art to be involved in sodium balanced in the heart and kidneys. See page 2 of the instant specification. Thus, the claims are considered broad because they embrace increasing BNP in any organ (heart, kidney, brain, etc.) of a mammal and determining the result of the increase of BNP in the mammal. The instant specification only provides sufficient guidance for determining whether the increase of BNP delays the progression of ALVD in a canine model. The instant specification does not teach one skilled in the art how to practice the claimed invention in a genus of mammals. See MPEP 2164.08, which recites, "The focus of the examination inquiry is whether everything within the scope of the claim is enabled. The Federal Circuit has repeatedly held that the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." See In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In addition, the specification lacks sufficient guidance and/or factual evidence for the skilled artisan to determine without undue

experimentation what animal models (model for hypertrophy, hypertension, heart failure, kidney failure, etc.) other than ALVD canine model can be used in the claimed method and such information cannot be obtained in the prior art without undue experimentation. Each model may or may not be affected by increasing the level of BNP. The prior art teaches that BNP is primarily a ventricular hormone that is synthesized and secreted constitutively in an adult (LaPointe et al., Hypertension, 715-722, 1996, cited on a previous PTO-892). It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (19663, Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

Furthermore, and with respect to claims directed to any gene therapy treatment of a mammal; the state of the art exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any gene therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). For additional reviews of the unpredictability of gene therapy art, see Kmiec, American Scientist, 1999, 87, 240-247; Juengst, BMJ, 2003, 326:1410-11; Orkin et al., December 7, 1995, "Report and Recommendation of the

Panel to Assess the NIH investment in Research and Gene Therapy", issued by the National Institute of Health.

In addition, Askari et al., Seminars in Thoracic and Cardiovascular Surgery, 14:167-177, 2002, teaches the unpredictability for the gene therapy treatment of heart failure in a mammal.

Therefore, at the time the application was filed, the state of the art for gene therapy was considered unpredictable.

With respect to the working examples, the applicant contemplates locally (catheter-based to the heart) and systemically (intramuscular) delivering a nucleic acid encoding BNP in normal canines. The specification recites that catheter-based, adenoviral gene transfer of human BNP in dogs resulted in local and systemic BNP 3 days after infection. Furthermore, the applicant contemplates establishing whether local or systemic BNP delays the progression of ALVD to overt congestive heart failure (CHF) in a canine ALVD model. The ALVD model has progressive ventricular systolic dysfunction with ventricular dilatation and hypertrophy. In view of the definition of the ALVD model, the ALVD model is in the initial stage of heart failure (page 45, lines 17-21). The specification does not teach any BNP gene therapy method, including a method to inhibit or prevent heart failure in mammal or a BNP gene therapy method to relax cardiac muscle in a mammal. At the time the application was filed, the prior art is absent for any method of BNP gene therapy.

In addition, with respect to the amount of guidance provided, the applicant teaches how to locally and systemically express BNP for 3 days in a normal dog using catheter-based, adenoviral gene transfer of human BNP. However, the relevance of this data to practicing the genus of methods embraced by the claims is unclear at best because neither applicant nor the

prior art provide a correlation or nexus between the data obtained in the *in vivo* study in a normal dog as those provide by applicant to practicing the claimed invention without an undue amount of experimentation. The applicants do not teach what amount of BNP expression is considered therapeutic or what organs besides the left ventricle of the heart are effected by increasing BNP expression in a mammal. The skilled artisan would be required to perform trial and error experimentation to determine what amount of BNP expression would be required in any mammal to produce a therapeutic result that is encompassed by the claimed invention or what happens when BNP is expressed in other organs besides the left ventricle of the heart. In addition, with respect to the prophetic examples, in view of the lack of guidance provided by the specification for sufficient guidance and/or factual evidence for practicing the claimed methods and the unpredictability of gene therapy, the specification does not teach one skilled in the art how to practice the claimed invention without an undue amount of experimentation. Given the above analysis of the factors, it is concluded that the skilled artisan, at the time the application was filed, would have to conduct an undue amount of experimentation in order to practice the full scope of the claimed invention.

In addition, with respect to claims 3, 17-23, and 25-29, the claims encompass using a genus of administration routes in the claimed methods. Claims 3, 17, 18, 22, 23, and 25-26 embrace using any route of administration. Claims 19, 20, 28, and 29 embrace using local administration to the heart. Claim 21 embraces using systemic administration. Claim 27 embraces administration to the skeletal muscle of a mammal. With respect to using a genus of administration routes in the claimed methods, the specification does not provide sufficient guidance and/or factual evidence for using the genus of administration routes. In view of the

unpredictability in the art of record and the prior teaching that the left ventricle is the only part of an organ of a mammal associated with BNP expression, one skilled in the art could not reasonably predict without undue experimentation why one skilled in the art would want to delivery BNP to a genus of organs or what route other than local would deliver the composition to the heart. For the reasons set forth above, even if the composition is delivered to the heart, the as-filed specification does not teach one skilled in the art what amount of the expressed BNP is considered to be therapeutically effective for any claimed methods using local administration. Furthermore, with respect to claim 27 directed to delivering the composition to the skeletal muscle of the mammal, the specification does not provide sufficient guidance and/or factual evidence for how BNP expression in the skeletal muscle reasonably correlates to sufficiently expressing BNP in the heart to inhibit or prevent heart failure or relax cardiac muscle in a mammal. In addition, the prior art is absent for teaching the skilled artisan what would happen when the level of BNP is increased in the skeletal muscle and the specification does not teach the skilled artisan how to use a method comprising increasing BNP levels in the skeletal muscle of a mammal. The art of record does not teach one skilled in the art how to express a therapeutic amount of BNP in the heart of a mammal by administering a composition encoding BNP to the skeletal muscle of the mammal. As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed compositions generate a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any gene therapy method as contemplated by the claims, particularly given the unpredictability of gene therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the art of record, at the time the invention was made, only provide sufficient guidance and/or factual evidence for increasing BNP levels to establish whether overexpression of BNP delays the progression of asymptomatic left ventricular dysfunction (ALVD) in a canine ALVD model to overt congestive heart failure (CHF) comprising intracoronary delivery to the canine a composition comprising a nucleic acid encoding BNP operatively linked to a promoter in a delivery vehicle and determining whether the increase of BNP delays the progression of ALVD in the model and do not provide sufficient guidance and/or evidence to reasonably enable the full breadth of the claimed invention. Given that gene therapy wherein any delivery vehicle is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any delivery vehicle cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Applicant's arguments filed 2/10/05 have been fully considered and they are found partially persuasive.

Applicant argues that applicant disagrees the interpretation by examiner that there is only one use for increasing BNP in a mammal is for inhibiting or preventing heart failure in a mammal or to relax cardiac muscle in a mammal. Applicant's specification provides multiple uses for such a method (Pages 46, lines 23-25). A person of ordinary skill in the art reading applicant's specification would have been able to practice the presently claimed invention to achieve such a purpose without undue experimentation given that the specification discloses that

injecting an adenoviral vector encoding BNP into the left ventricular myocardium not only increases coronary sinus BNP levels but also central nervous BNP levels.

Applicant's argument is found partially persuasive because the applicant teaches another use of the claimed methods. Applicant teaches increasing BNP levels to establish whether overexpression of BNP in a canine ALVD model to overt CHF (pages 45-50).

However, as stated by applicant that the claimed method embraces several uses and the claims must be considered broad. For the reasons of record, the instant specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to practice the full breadth of the claimed invention.

Applicant's argument is not found persuasive because the limitations "increasing BNP levels to establish whether overexpression of BNP delays the progression of asymptomatic left ventricular dysfunction (ALVD) to over congestive heart failure (CHF)" and "injecting an adenoviral vector encoding BNP into the left ventricular myocardium not only increases coronary sinus BNP levels but also central nervous BNP levels" argued by applicant are not set forth in the claimed methods. In addition, if the claimed methods are directed to establish whether overexpression of BNP delays ALVD, the claimed methods are missing steps required for one skilled in the art to practice the claimed invention.

In addition, Applicant argues that the adenovirus can be used to increase plasma BNP levels following systemic administration as evidenced by Pan et al. (Am. J. Physiol. Heart Circ. Physiol. 286:H2213-2218, 2004). In addition, applicant asserts that there is no undue experimentation to make a nucleic acid molecule encoding BNP and administer that nucleic acid molecule to a mammal to increase BNP levels.

With respect to applicant's argument that a post-filing reference (Pan, 2004) displays that adenoviruses can be used to increase plasma BNP levels following systemic administration, the argument is not found persuasive because the claims are directed to using a composition to deliver the BNP to a mammal, including adenovirus. In view of the prior art, one skilled in the art cannot reasonably extrapolate from the teachings in the specification to practicing the claimed method using a genus of administration routes. While, it is acknowledged that other types of gene therapies have been cited in the art as treating a particular disease or genetic disorder using distinct material and methods, the art of record teaches that one skilled in the art can not reasonably extrapolate from one type of gene therapy to another type of gene therapy without an undue amount of experimentation and the art of record teaches that there is no universal protocol that can be reasonably extrapolated from one type of gene therapy to the claimed gene therapy method (See Verma, Anderson, Rosenberg et al, and Rubanyi).

In addition, it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997) and (In Enzo 188 F.3d at 1374, 52 USPQ2d at 1138). On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of using a compound comprising a nucleic acid encoding a BNP protein, for those skilled in the art to experiment with level of expression BNP, so as to provide a therapeutic method as intended by the as-filed specification at the time the invention was made.

Furthermore, the post-filing reference does not use the same materials and methods as embraced by the claimed methods or disclosed in the instant specification. This would indicate

to one skilled in the art that there are materials and methods steps not disclosed in the specification that are required for practicing the claimed invention. In addition, the article was published five years after applicant filed his application (provisional filed on 5/24/99).

With respect to applicant's assertion that there is no undue experimentation to make a nucleic acid molecule encoding BNP and administer that nucleic acid molecule to a mammal to increase BNP levels. Applicant's assertion is not found persuasive because the enablement rejection is not directed to making a nucleic acid encoding BNP. The enablement rejection is based on several factors, including the prior art teaching the BNP expression is only observed in the left ventricle of the heart of a mammal, the unpredictability of nucleic acid expression in vivo using a genus of administrations routes and delivery vehicles, the unpredictability of increasing BNP levels in any organ other than the heart and determining what happens (See Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997); and the lack of guidance for using the claimed method to treat a disease and/or disorder associated with BNP. In view of the analysis of the factors, the specification does not provide sufficient guidance and/or factual evidence for using the full scope of the claimed invention. In addition, the assertion is not found persuasive because other than the assertion, the applicant provides no guidance and/or evidence to support these assertions. Therefore, applicant's assertions regarding are not compelling. See MPEP § 2145 and 716.01(c).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The instant claims read on increasing brain natriuretic peptide (BNP) levels in a mammal comprising administering a composition comprising a promoter operatively linked to a nucleic acid encoding BNP.

Claims 3, 20, 22, 23, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olson (US 2002/0100069).

Olson teaches generating transgenic animals using an expression construct comprising a cardiac hypertrophy gene such as BNP (beta-type natriuretic peptide, also known as brain natriuretic peptide) operably linked to a promoter (pages 6, 7, and 9). In addition, Olson teaches the limitation in instant claim 29 because a catheter is required to deliver the expression construct to embryos. Olson teaches the claimed method because the claims do not limit when the expression construct is delivered to a mammal. Thus, the nucleic acid can be delivered at any time point in the mammal's life span including embryonic development, which is part of a method of generating transgenic mammals (pages 6-7).

However, Olson does specifically teach the method steps involved in making a transgenic mammal comprising a nucleic acid encoding BNP, which would result in increasing the level of BNP in the mammal. In addition, Olson does not specifically teach using a plasmid comprising a nucleic acid encoding BNP in aqueous solution in the method.

However, at the time the invention was made, Olson teaches using a variety of cardiac genes (including cardiac hypertrophy genes such as BNP and MHC) for producing a transgenic animal and monitoring their expression (pages 7 and 9). Olson teaches that BNP decreases blood pressure by vasodilation and natriuresis (page 6). Olson teaches steps for producing transgenic mice, which includes microinjecting DNA (plasmid) in a solution into embryos (pages 6-7). Olson further teaches that the transgenic mice can be used to screened compounds useful for treatment of heart disease (page 7).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to used the transgenic method taught by Olson, namely to generate a transgenic mouse comprising an expression construct comprising a BNP gene product which would result in an increase in BNP levels in the transgenic mouse. One of ordinary skill in the art would have been motivated to use the method of producing a transgenic mammal taught by Olson to study the over-expression of BNP in the heart of the transgenic mouse because over-expression of BNP is involved in cardiac hypertrophy in a mammal as taught by Olson (page 6).

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to used a plasmid comprising the BNP nucleic acid in an aqueous solution in the transgenic method taught by Olson, namely to increase BNP levels in a transgenic mouse. One of ordinary skill in the art would have been motivated to use the plasmid

in aqueous solution in the method taught by Olson because one of ordinary skill in the art understands that a plasmid in aqueous solution is the conventional material used for introducing DNA into embryos in a method to produced transgenic mice.

Claims 3, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olson (US 2002/0100069) as applied to claims 3, 20, 22, 23, and 29 above, and further in view of Readhead et al (US 6,316,692).

However, Olson does not specifically teach using adenoviral vectors comprising a nucleic acid encoding BNP in the method of generating transgenic mammals or where the delivery vehicle is a recombinant adenovirus.

However, at the time the invention was made, Readhead teaches that adenovirus comprising an adenoviral vector were readily available for use for one of ordinary skill in the art for generating transgenic animals (mice) (columns 2-4, 8, and 11-12). Readhead teaches that a method using an adenoviral vector is less costly, faster and more efficient approach to producing transgenic animals (column 4).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Olson and Readhead, namely to use an adenovirus comprising an adenoviral vector comprising a nucleic acid encoding BNP in a method of generating a transgenic mammal. One of ordinary skill in the art would have been motivated to use the method of producing a transgenic mammal as taught by Readhead because Readhead teaches that the method is less costly, faster, and more efficient approach to producing transgenic mammals compared to conventional methods of producing transgenic mammals.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 3, 25, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olson (US 2002/0100069) as applied to claims 3, 20, 22, 23, and 29 above, and further in view of Seilhamer et al. (AGGGG) and Kambayashi et al. (cited on a previous PTO-892).

However, Olson does not specifically teach using either canine or human cDNA BNP in the method of generating transgenic mammals.

However, at the time the invention was made, Seilhamer teaches that cDNA for porcine, canine, and human BNP were readily available for use for one of ordinary skill in the art (page 650). In addition, Kambayashi teaches that cDNA for porcine, canine, and human BNP were readily available for use for one of ordinary skill in the art (page 599).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Olson and Seilhamer and Kambayashi, namely to use cDNA from either canine BNP or human BNP in a method of generating a transgenic mammal. One of ordinary skill in the art would have been motivated, as a matter of designer's choice, to use either cDNA encoding canine BNP or cDNA encoding human BNP in the method to study the expression of either species of BNP in the heart of a transgenic mammal. In addition, one of ordinary skill in the art would have been motivated to use either cDNA in the method since both cDNAs were readily available to one of ordinary skill in the art and to avoid the laborious processes involved in gene identification, mapping, and cloning of a gene encoding BNP.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
Patent Examiner, Group 1635